

REMARKS

In the application, claims 2-15 and 23-29 are pending and rejected. The Examiner has withdrawn the requirements for species elections relative to the different analysis steps and the different agents. As a result, claims 8, 15, 23 and 24, which were previously indicated to be withdrawn, are included in the claim listing. After due consideration of the Examiner's comments in the Office Action of March 26, 2004, the claims have been amended to more clearly set forth what Applicants regard as their invention. Applicants respectfully request reconsideration of the claims as amended.

The title has been amended to more closely reflect the subject matter of the elected claims.

The Examiner objects to claim 25 as having improper dependency from a cancelled claim. Further, the Examiner objects to informalities in the claims arising from missing or incorrect language. Each cited incident has been corrected by amendment.

Rejections under §112

The Examiner rejects claims 2-10 and 26-29 under 35 U.S.C. §112, 1st para., as failing to comply with the enablement requirement.

With regard to claim 6, the Examiner comments that it would not be possible to assess gene response after their responses had been averaged.

Claim 6 has been amended to clarify that the step of averaging is for determination of background signal intensity for establishing a threshold for detectability so that only those signals that exceed the threshold will be used for further analysis.

With regard to claims 1 and 26, the Examiner questions the how one can directly expose polynucleotides to a toxic compound.

Claims 1 and 26 have been amended to clarify that tissue samples are exposed to the toxic compounds and the genes come from these tissue samples. This amendment is supported in the specification, for example, at page 27 in the paragraph beginning at line 3.

Claims 2-11, 13-15, and 23-29 are rejected under 35 U.S.C. §112, 2nd para., as being indefinite. In particular, the Examiner comments that the step of assessing toxicity is omitted.

Each of the base claims has been amended to include the step of assessing toxicity.

Rejections under §103

Claims 2-5, 7-9, 11-14, 24 and 25 are rejected under 35 U.S.C. §103(b) as being unpatentable over Cunningham et al. (Pat. No.6,160,105) in view of Hilsenbeck et al. (*J. Nat'l Cancer Inst.* V. 91, pp. 453-459 (1999)). Cunningham et al. discloses the use of clusters of EST sequences in conjunction with a toxicological analysis. Hilsenbeck shows the use of principal components analysis (PCA). The Examiner states that it would have been obvious to combine the two references to use PCA to analyze gene expression data to determine the gene sets that are most varied by the treatment and to vary dose as well as time of treatment.

Applicants respectfully submit that the clustering described by Cunningham et al. is not a statistical analysis of gene expression data but rather a sequence matching exercise in which the sequences of two or more ESTs are compared to determine whether the sequences have any overlap. If overlap is found, the ESTs are grouped together into "master clusters" after which a representative clone of the master cluster was "nominated" for further processing. There is no statistical analysis of the resulting data that would produce a numerical value that would be useful for further analysis for assessment of toxicity. The "clustering" used by Cunningham et al. is completely distinct from the statistical analysis of hybridization intensity measurements disclosed by Applicants. The statistical method of cluster analysis utilized according to the present invention, and the alternative contrast analysis, are techniques for creating composite variables for providing a measure of variation within the data. This analysis is performed on the hybridization signal intensity measurements; it has nothing to do with the sequence analysis or pairwise DNA comparison as taught by Cunningham, et al.

Hilsenbeck, et al. teaches the application of PCA for use in data reduction and identification of significant outlier genes. PCA is applied directly to the raw data generated by cDNA microarray expression profiling for the purpose of reducing the amount of data that might be considered relevant. Neither Hilsenbeck, et al. nor Cunningham et al, provide any teaching or suggestion to combine two separate statistical techniques in sequential order to generate a single composite variable, or measure of similarity, which can be used for comparison. Cunningham, et al.'s method is arguably not even statistical. It certainly does not lead to an *in silico* analysis of gene expression data as does Applicant's invention. Hilsenbeck et al. at best disclose a single

statistical method. Accordingly, it is respectfully submitted that the combination of Cunningham, et al and Hilsenbeck, et al cannot render Applicant's invention obvious because it fails to teach any sequence of statistical methods for generating a single composite variable or measure of similarity that can be used to indicate toxicity.

The Examiner rejects Claims 11 and 15 under 35 U.S.C. §103(b) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. and further in view of Holden, et al. Holden et al. are cited for their teaching of treatment of a hepatoma cell line with CCl₄.

It is submitted for the reasons set forth above that the combination of Holden et al. with the Cunningham et al and Hilsenbeck et al. references fails to add what is missing from the previously-discussed combination. Specifically, there is no teaching or suggestion of the use of multiple statistical analyses in a sequence to generate a single composite variable or measure of similarity that can be used in a comparison. Accordingly, Applicants respectfully submit that the subject matter of claims 11 and 15 is not made obvious by the cited combination.

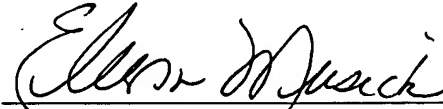
It is submitted that the foregoing amendments and arguments address and overcome each ground for rejection. Therefore, Applicants respectfully request that the Examiner withdraw the rejections and objections to the claims and allow all claims as now presented and issue a notice of allowance of the application.

Should the Examiner believe that prosecution of this application might be expedited by further discussion of the issues, he is invited to telephone the undersigned attorney for Applicants at the telephone number indicated below.

Respectfully submitted,

Dated: September 20, 2004

By:



Eleanor M. Musick
Attorney for Applicants
Registration No. 35,623

PROCOPIO CORY HARGREAVES & SAVITCH LLP
530 B Street
Suite 2100
San Diego, California 92101-4469
Telephone: (760) 931-9703 (direct)
Facsimile: (760) 931-1155

Docket No. 4000-US (111944-000001)